A DRUG NAME: VINORELBINE

SYNONYM(S): didehydrodeoxynorvincaleukoblastine, vinorelbine tartrate

COMMON TRADE NAME(S): Navelbine® (Glaxo Wellcome)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Vinorelbine, a semi-synthetic vinca alkaloid, exerts its anti-tumour activity by binding to tubulin and inhibiting microtubule assembly, thereby preventing cell mitosis and causing cell death. It is cell cycle phase-specific.

Oral Absorption	Yes, 40% bioavailable	
Distribution	Initial rapid decline in plasma concentration after IV administration due to distribution to peripheral compartments (spleen, liver, kidneys, lungs, thymus, heart, and muscles) and metabolism; therafter a prolonged terminal half life	
	cross blood brain barrier?	Minimal
	PPB	70-80% (not sure where this comes from)
Metabolism	Largely metabolised via hepatobiliary system	
	active metabolite(s)	Yes, deacetylvinorelbine
	inactive metabolite(s)	Yes, N-oxide vinorelbine
Excretion	Mainly eliminated by the liver, with approximately 40% of drug being recovered in the feces.	
	Urine	<20% (unchanged)
	$T_{1/2}$	27.7 – 43.6 hrs

C INDICATIONS AND STATUS

*Advanced non-small cell lung cancer
*Metastatic breast cancer after standard first-line chemotherapy or relapse < 6 months of anthracycline-based adjuvant therapy.

*Therapeutic Products Programme, Health Canada approved indication

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT		ONSET
Cardiovascular	Chest Pain (5%)	I	
Central nervous System	Headache (5%)	I	
Dermatologic	Mild alopecia (12%), complete (8-11%*)		E
	Radiation recall reaction		E
	Rash (5%)		E
Extravasation hazard (refer to Appendix 2)	**Vesicant**	I	
	Phlebitis (30%) (2% severe)	I	
Gastrointestinal	Nausea (32 to 50%*;severe <1%)	I	
	Vomiting (20%)	I	
	Constipation (28-38%*)	I	
	Anorexia (16-19%*)		E
	Diarrhea (13-20%*)		E
	Stomatitis (15-16%*)		E
Hematologic	Granulocytopenia (Grade 3-4 66%) Nadir 7-10days, recovering in following 7-14 days		E
	Grade 3 or 4 anemia (1-14%*)		E
	Grade 3 or 4 thrombocytopenia (<1%)		E
Hepatic	Transient, asymptomatic elevation of liver enzymes (62%) and total bilirubin (10%)		E
Injection site	Erythema, pain, vein discoloration, & phlebitis (33%), severe local reactions seen in only 2%	I	
Musculoskeletal	Back or jaw pain, myalgia, arthralgia (5%)	I	

D ADVERSE EFFECTS (continued)

ORGAN SITE	SIDE EFFECT	ONSET
Neurologic	Mild-moderate peripheral neuropathy (10-20%*)	I
Pulmonary	Shortness of breath (5%)	I
	Bronchospasm (3%)	I
Renal/ metabolic	Syndrome of inappropriate ADH secretion (<1%)	E
Systemic Effects	Asthenia (25-41%*)	E
	Fever (10-19%*)	E

Dose-limiting side effects are underlined.
I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

*Different toxicity incidences were experienced in treatments of advanced breast cancer and metastatic non-small cell lung cancer, thus percentages of incidence are presented in "range".

Chest Pain, possibly accompanied by changes in electrocardiogram, is reported in 5% of patients, mostly in those with previous history of cardiovascular disease or presence of a bulky tumour within the chest. There are reports in the literature of myocardial ischemia and infarction, which may have been related to vinorelbine.

Neurotoxicity is generally mild to moderate, demonstrated by limited, decreased or total loss of osteotendinous reflex. It is generally reversible on drug discontinuation. Severe neurotoxicity is seen in less than 1% of patients. Prior treatment with paclitaxel or other neurotoxic drug, or the presence of pre-existing neuropathy of any etiology, may result in accumulated neurotoxicity, requiring discontinuation of vinorelbine therapy.

Paralytic ileus and paresthesia have been reported (2% and rarely, respectively). Discontinue vinorelbine if neurotoxicity is moderate or severe. **Asthenia**, usually mild or moderate, tends to increase with cumulative dosing.

Granulocytopenia is dose-limiting and results in febrile neutropenia or infections in 8-9% of patients, and is fatal in 1% of patients..

Elevated liver enzymes were observed frequently in vinorelbine treatment. Elevated aspartate aminotransferase and alanine aminotransferase were seen in approximately half of 327 breast and non-small cell lung cancer patients who participated in three separate clinical trials. Patients were asymptomatic and did not require discontinuation of vinorelbine. Six percent of the same patient group developed elevated total bilirubin levels (grade 3 or 4). Elevated alkaline phosphatase levels (grade 3 or 4) were seen in 26% of patients, although these elevations might possibly have been related to liver or bone metastases in this group of patients.

Injection site reactions, such as pain, erythema, or vein discolouration are common (30% of patients) but severe in only 2% of patients. Phlebitis is seen in approximately 6 % of patients. Long infusion times (i.e. more 20 minutes) may increase the risk of phlebitis and injection site reactions. Flushing the vein before and after administration of vinorelbine can also reduce these reactions. One study has shown that the incidence of phlebitis can be reduced by infusing dexamethasone IV immediately following the administration of vinorelbine.

D ADVERSE EFFECTS (continued)

Back pain has been reported if infusion duration of vinorelbine is too short (i.e. less than 6 minutes).

Acute shortness of breath and severe bronchospasm have been reported (severe in only 2% of patients). Incidence is infrequent but seen more commonly when Vinorelbine or other vinca alkaloids are combined with mitomycin. Aggressive treatment of symptoms with bronchodilators, steroids and /or oxygen may be required, especially in patients with pre-existing pulmonary dysfunction.

E DOSING

Adult:
Intravenous: 30mg/m^2 given once weekly. May be given for 3 weeks or 2 weeks followed by a one week rest period.

Dosage in myelosuppression:

Absolute neutrophil counts (X10^9/L)	% initial dose
≥= 1.5	100%
1 – 1.499	50%
< 1	hold dose; repeat count in 1 week reduce initial dose by 25% if ≥ 3 week recovery period or febrile neutropenia occurred

Dosage in renal failure: no adjustment required

Dosage in hepatic dysfunction: There is no evidence that the toxicity of Vinorelbine is increased in patients with transaminases increases, but as Vinorelbine undergoes hepatobiliary metabolism and excretion, administer with caution in hepatic insufficiency, especially with hyperbilirubinemia

Suggested Adjustments for increases in total bilirubin:

Total bilirubin (umol/L)	% usual dose
< 2 x ULN	100%
2-3 x ULN	50%
> 3 x ULN	25%

Geriatric population: no specific dosage adjustments are required for increased age.

Children: safety and efficacy not established

F ADMINISTRATION GUIDELINES

- Mix in 50mL minibag (D5W, NS) to a final concentration 0.5-2mg/mL; Infuse over 6-10 minutes through free-flowing IV
- May push (at final concentration of 1.5 – 3mg/mL) through sidearm of free flowing IV (NS); Inject over 6-10 minutes

- After administration is completed, flush IV line with 200 to 300ml NS or D5W

G SPECIAL PRECAUTIONS

Vinorelbine should be administered only via the iv route; intrathecal administration is fatal. Vinorelbine may result in radiosensitizing effects with prior or concomitant radiation therapy. Vinorelbine is potentially **mutagenic** and **carcinogenic**. Vinorelbine may cause fetal harm when administered to **pregnant** women. **Breast feeding** in not recommended.

H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Mitomycin	Acute pulmonary effects	Unknown	Bronchodilators, steroid and/or oxygen; use in combination with mitomycin with extreme caution
Paclitaxel /other neurotoxic compounds	Neuropathy	Additive spindle toxicity (speculated)	Discontinue vinorelbine
Cisplatin	Grade 3 and 4 granulocytopenia (79% incidence)		Dose adjustments
Radiation	Sensitises effects – may see radiation recall		Use with caution

I RECOMMENDED CLINICAL MONITORING

<u>Recommended</u> Clinical Monitoring

- Monitor blood counts at each visit
- Baseline liver function tests
- Routine toxicity (especially neurotoxicity and local toxicity) assessment

<u>Suggested</u> Clinical Monitoring

- Periodic liver function tests
- Local site toxicity ratings, if incident of phlebitis

REFERENCES:

Moore, M. Drug Monograph: Vinorelbine (draft) for BCCA:The Cancer Drug Manual. Vancouver . August 29th, 1996. (monograph not reviewed by Editorial Review Board)

Ginopoulous P, Matronikolis NS, Karana A et.al: Use of dexamethasone in the management of phlebitis caused by intravenous of vinorelbine (Nalvelbine). Medical Science Research 1998;26: 397-8.

Glaxo Wellcome Inc. Navelbine product monograph. Missisauga, Ontario. 1996: May.

Gregory RK, Smith IE. Vinorelbine – a clinical review. British J Cancer (2000) 82(12), 1907-13.

Jones SF, Burris HA. Vinorelbine: A new antineoplastic drug for the treatment of non-small cell lung cancer. Ann Pharmacother 1996; 30: 501-06.

McEnvoy G. (editor) : American Hospital Formulary Drug Information 2000. Bethseda : American Society of Health-System Pharmacists, 1090-4.

Toso C, Lindley C. Vinorelbine: A novel vinca alkaloid. Am J Health-Syst Pharm. 1995; 52: 1287-304.

Welbanks L. (editor) : Compendium of Pharmaceutical and Specialties 35th ed. Ottawa: Canadian Pharmaceutical Assoication, 2000: 1022-4.

Zhou XJ, Rahmani R. Preclinical and clinical pharmacology of vinca alkaloids. Drugs 44 ,(Suppl 4): 1-16. 1992.